이학석사 학위논문

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서울대학교 융합과학기술대학원

분자의학 및 바이오제약 전공

노 은

**A thesis of the Degree of Master of Philosophy**

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**April 2019**

**The Department of Molecular Medicine and**
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**Graduate School of Convergence Science and Technology,**
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지도교수 윤 홍 덕

이 논문을 이학석사 학위논문으로 제출함

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노 은의 이학석사 학위논문을 인준함

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위 원 장 _____ (인)

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# The inhibitory effect of IL1RN on cytokine production in oncogene induced senescent cells

**by**

Eun Ro

**A thesis submitted to the Department of Molecular Medicine and Biopharmaceutical Sciences**
**in partial fulfillment of the requirements for the Degree of Master of Philosophy in Science at Seoul National University**
**Graduate School of Convergence Science and Technology, and College of Medicine or College of Pharmacy**

**June 2019**

**Approved by Thesis Committee:**

**Professor** _____ **Chairman**

**Professor** _____ **Vice chairman**

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# ABSTRACT

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Cellular senescence has been studied for a long time. However, the mechanisms which control and regulate the process of cellular senescence have nearly been identified. Not only by replicative senescence which is triggered sorely depending on time, this study focuses on defining gene regulation mechanism which finally induces cellular senescence and precipitates aging process. We first analyzed mRNA levels of Interleukin-1 receptor antagonist (IL1RN) and Senescence Associated Secretory Protein (SASP) factors by days in Oncogene Induced Senescence (OIS) system. It was found out that the expression of IL1RN progressively increases and suddenly decreases in the late passage. We thought that if the expression did not decrease in the late passage, maybe the senescence process would have been attenuated. Additionally, it was identified that the expressions of other SASP factors such as IL1α, IL1β, IL6 and IL8 related to IL-1 signaling and NF-κB pathway progressively increased till the end of time point. However, the secretion of them were dramatically reduced when rIL1RN was added and in IL1RN over-expressing cells, which concluded that IL1RN regulates the secretion of them. We also showed that gene

regulation by IL1RN can affect senescence attenuation through SA-β gal assay. This study gives possibility that inhibition of SASP factors can attenuate senescence.

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**Keywords: IL1 signaling, IL1RN, Cellular senescence, SASP**

**Student number: 2016-26873**

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| | |
|---|---|
| IL1 | Interleukin1 |
| IL1α | Interleukin1α |
| IL1β | Interleukin1β |
| IL6 | Interleukin6 |
| IL8 | Interleukin8 |
| IL1RN(IL1Ra) | Interleukin1 receptor antagonist |
| OIS | Oncogene Induced Senescence |
| SASP | Senescence Associated Secretory Phenotype |
| NF-κB | Nuclear factor kappa chain-enhancer of activated B cells |
| SA-βgal | Senescence associated beta galactosidase |
| P | Passage |
| hIL1RN | human IL1RN |
| ROS | Reactive oxygen species |
| p38MAPK | p38 mitogen-activated protein kinases |
| mTOR | mammalian target of rapamycin |
| DDR | DNA-damage response |
| C/EBPβ | CCAAT enhancer-binding protein beta |
| IL1R | Interleukin 1 receptor |
| MyD88 | Myeloid differentiation primary response 88 |
| IRAK1 | Interleukin-1 receptor-associated kinase 1 |
| IRAK4 | Interleukin-1 receptor-associated kinase 4 |
| IL-1AcP | IL-1R accessory protein |
| TNF | Tumor necrosis factor |
| PD | Population Doubling |
| ER | Estrogen Receptor |
| 4-OHT | 4-Hydroxytamoxifen |

| | |
|---|---|
| qRT-PCR | Quantitative real-time PCR |
| rIL1RN | recombinant IL1RN |

# I. INTRODUCTION

## 1-1. The functions of SASP in cellular senescence

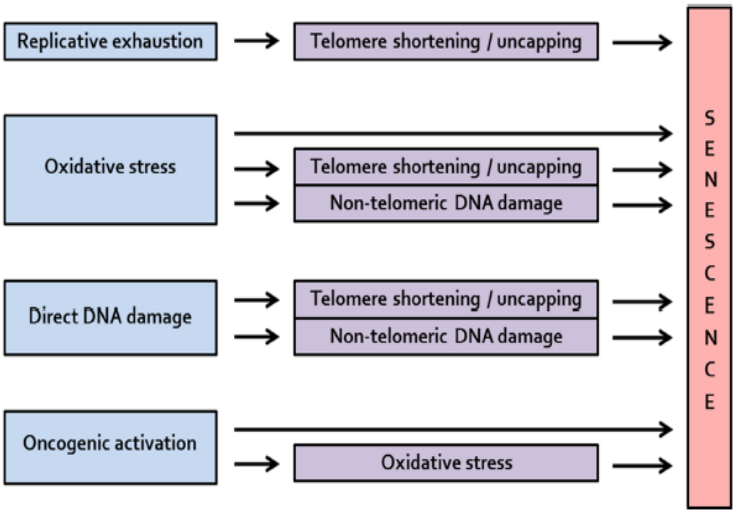


**Figure 1-1-1. The common causes of cellular senescence and their interconnection.**

Cellular senescence is a process in which cells stop proliferating and go through distinctive phenotypic alterations, including chromatin and secretome changes, and tumour-suppressive role. Generally, 'senescence' means the cessation of replicative growth after extensive timely passaging in culture (Aravinthan et al., 2015). However, not only originating from replicative senescence, diverse stressors including malfunctioning telomeres, distorted chromatin and especially DNA damage profoundly attribute cellular senescence through p53 and RB tumor suppressor proteins (Campisi et al., 2005). and finally build a strong anticancer mechanism to prevent from unrestricted growth of damaged cells.

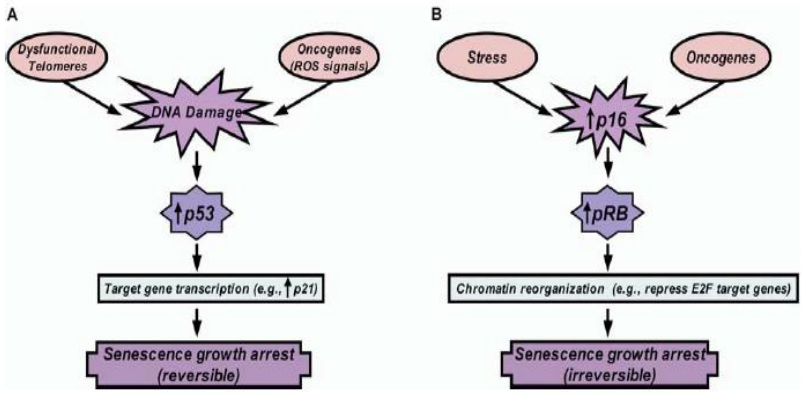


**Figure 1-1-2. Roles of the p53 and p16/pRB pathways in the senescence response**

The paradox that cellular senescence process can be an anti-tumorigenic and also can promote cancer progression at the same time can be explained by cell nonautonomous mechanisms. The main factor of secretome changes to cellular senescence can be said as secretory proteins such as a wide range of cytokines, chemokines, and proteases. This so called SASP or SMS explains the non-cell-autonomous role of senescent cells and their effectiveness on aging and age-related diseases. SASP factors are mainly induced by persistent DNA damages especially through ROS and oncogenic stresses. The pathways which were found as the regulators of SASP are p38MAPK, mTOR and DDR through activation of NF-κB. Interestingly, IL1 signaling was recently found to be an upstream effector of both NF-κB and C/EBPβ, followed by IL6 and IL8 induction **(**Orjalo et al., 2009; Hubackova et al.,.2012; Acosta et al., 2013). Furthermore, more recent study has found that IL1 and TGFβ can control senescence by activating oxidative stress and DNA damage (Acosta et al., 2013).

The roles of SASP factors related to interleukin can be separated into two different manners: autocrine manner to maintaining senescence and paracrine manner to reinforcing senescence.IL6 and IL8 respectively. Also, IL1β can draw senescence from normal cells.

## 1-2. The interplay of interleukins in induction of senescence(SASP)

Interleukin-1 (both α and β forms) is a main mediator of innate immunity and inflammation. The IL1 cytokine group contains 11 related molecules , wherein eight cytokines are ligands and three receptor antagonists. IL1Ra especially suppresses the activation of the similar receptors and thus is a suppressor of the activity of IL1.

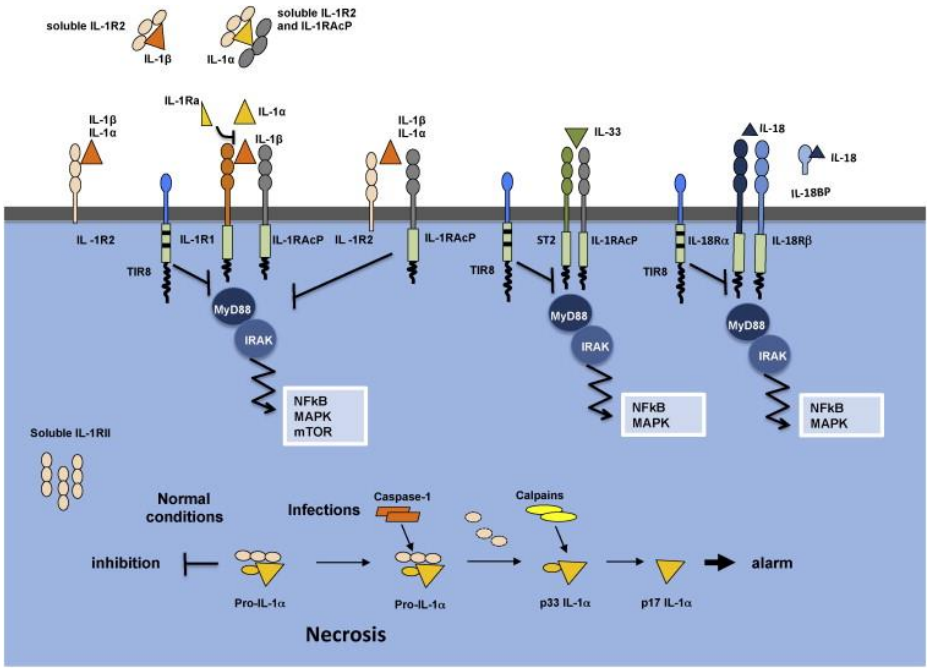


**Figure 1-2-1. Negative Regulators of the IL-1 Family**

Signaling from IL1 through IL1R is achieved by recruiting the MyD88 adaptor molecule, which is necessary for activating protein kinase IRAK1.

IRAK1 is activated by myeloid differentiation primary-response protein88 and IRAK4 to bind the IL-1R/IL-1AcP complex. IRAK4 then phosphorylates IRAK1, inducing nuclear translocation of NF-κB (Garlanda et al, 2013).

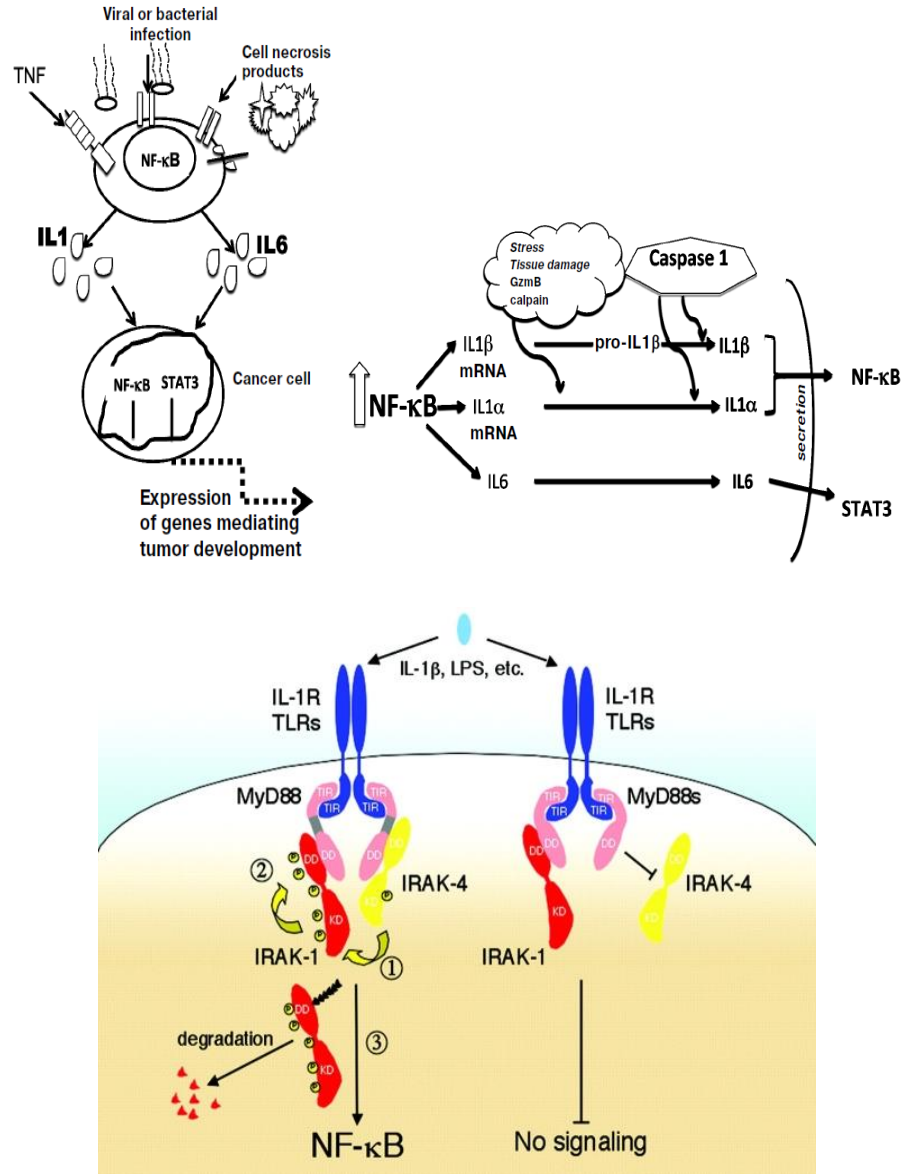


**Figure 1-2-2. Mechanisms of activation for oncogenic transcription factor NF-κB and NF-κB dependent mechanisms for synthesis and secretion of inflammatory cytokines such as IL1 and IL6**

Induced NF-κB finally drives the expressions of IL-6 and IL-8. NF-κB controls expression of diverse genes controlling pivotal functions related to oncogenesis and inflammatory cytokines such as TNF, IL23, IL1 and IL6 (Dmitrieva et al, 2016). The SASP is consist of the secretion of inflammatory cytokines, essentially IL-6 and IL-8, which explains many damaged and senescent cells express robustly high levels of IL-6 and IL-8. Not only as inflammatory mediators, they are also included to potent factors reinforcing senescence growth arrest.

## 1-3. The elimination of SASP as a therapy of aged-associated diseases

Senescent cells are situated in a subset of age-related pathologies and diseases, optional elimination of these cells can be an efficient therapy to remove the accumulation of many phenotypes affecting diverse tissues.

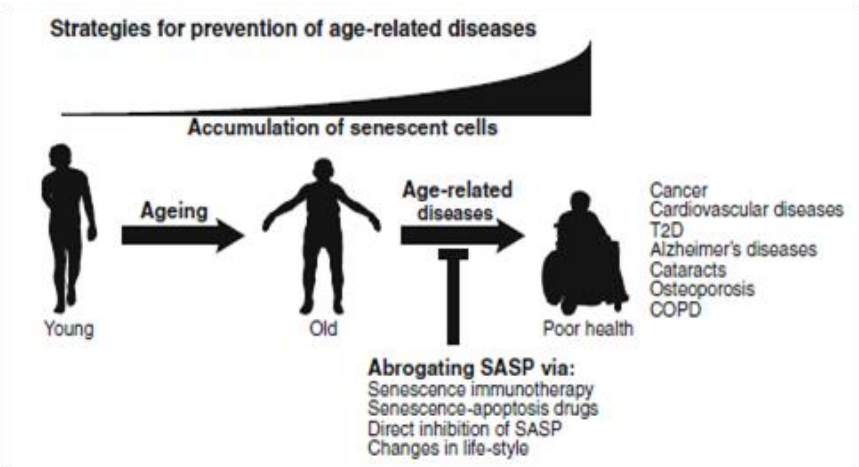


**Figure 1-3-1. Strategies for prevention of age-related diseases**

A group has shown that p16 insufficiency prolongs aging phenotypes in many tissues where p16 is activated (Baker et al, 2011). The group proved that the removal of p16-positive senescent cells delays age-associated phenotypes in those p16-sensitive tissues. As mentioned above, elimination of senescent cells can be a potential method for anti-aging therapy (Ovadya et al, 2014). Not only the removal of senescent cells, methods which can mediate SASP to inactivate inflammation could also be helpful for age-related diseases.

In a way of inhibiting or regulating SASP, this study focuses on IL-1Ra which is a potent inhibitor of ligands that binds IL-1R, rIL-1Ra inhibits binding of IL-1α and IL-1β from IL-1Rs, which finally can inhibit the subsequent production of other SASP factors. This study is assumed to help validate whether the interference of binding of IL1 by IL-1Ra to IL-1R can attenuate or alleviate aging process.

# II. MATERIALS AND METHODS

## 2-1. Cell culture and culture conditions

IMR90 cells were cultured on tissue culture dish. The medium was composed of DMEM media (GE health care) and 10% (v/v) fetal bovine serum (Gibco), suppled with 100units/ml penicillin, 100μg/ml streptomycin and 30μM ciprofloxacin (Sigma-aldrich).

## 2-2. Purification of recombinant protein

Active form of IL1RN cDNA could be obtained by PCR from full-length IL1RN gene purchased from KHGB(Korea human gene bank). The PCR product was inserted into pET-21a (Novagen). His6 fusion protein was expressed in the BL21DE3 strain and purified with Ni-NTA agarose (Qiagen) per the manufacturer's instructions.

## 2-3. Western blot assay

Cells were lysed with IP150 Buffer [150mM NaCl, 125mM Tris-Cl (pH 8.0), 0.1% NP-40, 10% glycerol, 1mM EDTA (pH 8.0)] and nuclear membrane was chopped by sonication (Bioruptor). Lysates were separated by SDS-PAGE and transferred onto nitrocellulose membrane for blotting using 25mM Tris-Cl, 250mM glycine, 15% (v/v) Methanol buffer at 4℃ for 2 hours. Membranes were blocked with 5% non-fat dry milk or BSA, 10mM Tris-Cl (pH 7.5), 150mM NaCl, 0.1% tween-20 for 1 hour. After blocking, membranes were washed 3 times and incubated with proper antibody at 4℃ for 16 hours.

Membranes were washed 3 times and incubated with HRP conjugated antibody at room-temperature for 1 hour. For detection, blots were reacted with ECL solution and exposed to X-ray film.

### 2-4. Antibodies

Anti-actin was purchased from Sigma; anti-IL1RA was purchased from Cell Signaling; anti-p53(DO-1) and anti-H-Ras(F235) were purchased from Santa Cruz.

### 2-5. Lentiviral infection and selection

For overexpression of H-Ras to induce senescence, ER:Hras cDNA which was obtained by PCR from retroviral pLNCX2-ER:ras purchased from Addgene was inserted into pLKO.1 lentiviral vector purchased from Sigma-Aldrich. For overexpression of extracellular IL1RN and GFP as a control, pLX301 Gateway-compatible lentiviral vectors encoding extracellular IL1RN and GFP were cloned. 293FT cell was used for lentivirus production by co-transfection of 1μg each of pLP1, pLP2, VSVG and 10μg of pLKO-ER:ras, pLX301-extracellular IL1RN, pLX301-GFP using Lipofectimine 2000 (Invitrogen). 48hrs after transfection, the virus-containing medium was collected and filtered through 0.45μm filters. Polybrene (10 μg/ml) was added just before target cell infection and infection was performed for overnight. 24hrs post infection, puromycin selection (1 μg/ml) was performed for 2 days. 100nM 4-OHT was added to growth media as a selective estrogen receptor modulator to induce H-Ras.

## 2-6. Quantitative real-time qPCR

Total RNA was extracted with TriZol® (Invitrogen) and reverse-transcribed using AMV Reverse Transcriptase (Sigma-Aldrich). mRNA and antibody-bound chromatin levels by chromatin immunoprecipitation assay were quantified by real-time qPCR with the SYBR® Green qPCR Kit (Finnzymes, F-410L) on the iQ5 and CFX Connect Real-time PCR Detection System (Bio-Rad) and then normalized to actin or 1% input chromatin using the 2-ΔΔ**C**T2-ΔΔCT calculation method. The sequences of the primers were described in Table 1.

## 2-7. SA-β gal assay

SA-β-galactosidase activity was assessed with the senescence β-galactosidase staining kit (Cell Signaling Technology) according with the manufacturer′s instructions. The percentage of senescent cells was the average number of stained senescent cells were counted randomly in each one experiment and divided by the total number of cells counted.

## 2-8. Statistics

Data are presented as means ± standard deviations, and P-values were calculated using the student's t-test calculator (http://www.physics.csbsju.edu/stats /t-test.html). A value of $p < 0.05$ was

considered to be statistically significant. All data are representative of at least 3 independent experiments.

| | Gene | 5’ primer | 3’ primer |
|---|---|---|---|
| Real-time PCR | 18s | GCTTAATTTGACTCAACACGGGA | AGC TAT CAA TCT GTC AAT CCT GTC |
| | *hIL1α* | TGAGACCAACCTCCTCTTCT | CCA GTA TCT GAA AGT CAG TGA TAG AG |
| | *hIL1β* | AATCTGTACCTGTCCTGCGTGTT | TGG GTA ATT TTT GGG ATC TAC ACT CT |
| | *hIL1RN* | GACCTGAGCGAGAACAGAAAG | CGC CTT CGT CAG GCA TAT T |
| | *hIL6* | GAGCTGTGCAGATGAGTACAA | GGA CTG CAG GAA CTC CTT AAA |
| | *hIL8* | AGACATACTCCAAACCTTTCCAC | TGAATTCTCAGCCCTCTTCAAA |

**Table 1. qRT-PCR primer list**

# Ⅲ. RESULTS

### 3-1. Cellular senescence can be induced by oncogene.

Cellular senescence is very important in molecular biological physiology. A number of cellular activities are closely affected by cellular senescence. Therefore, it is very important to understand mechanisms which can mediate or control ongoing process of cellular senescence progress. Not only by replicative senescence which can be induced by time passages, we've used estrogen receptor H-Ras oncogene virus to induce cellular senescence. By adding 100nM 4-OHT (Tamoxifen) in cell culture media by days, we could keep overexpressing H-Ras. Days were counted after adding 100nM 4-OHT into cell culture media. We could confirm that IMR90 cells in OIS system have become senescent (Figure 3-1-1) by SA-beta galactosidase staining assay results. The number of stained cells increased by days from day 0 to day 8. H-RAS overexpression could also be detected through western blotting, which supports that OIS was induced (Figure 3-1-2).

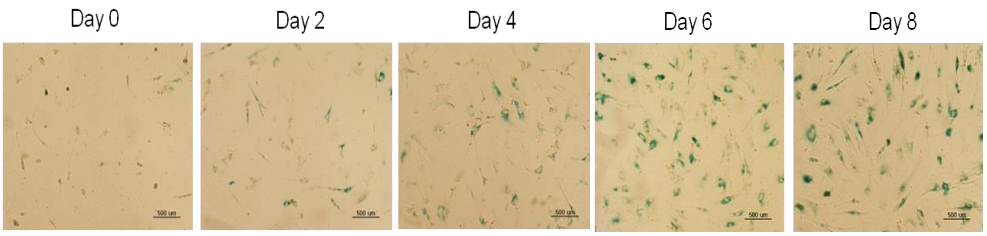


**Figure 3-1-1. IMR90 cells are induced senescent by H-Ras oncogene (10X, scale bar=500μm).**

IMR90 cells were infected by H-RAS oncogene expressing virus and then selected by puromycin (1μg/ml). The selected cells were induced senescent by 100nM 4-OHT. Senescence induced cells were stained by SA-beta gal assay and the degree of staining depended on days.

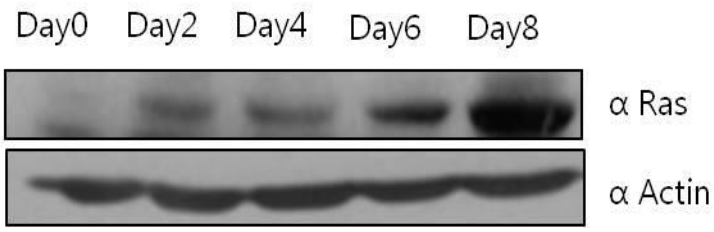


**Figure 3-1-2. Expression of H-Ras is probed in OIS system.**

Western blot analysis shows that IMR90 cells were induced senescent by H-Ras oncogene. It was probed by anti-H-Ras antibody. Days were counted after treating 100nM 4-OHT. Actin was used as contol.

### 3-2. IL1RN can regulate other SASP factors such as IL1α, IL1β, IL6 and IL8 in OIS system.

We first analyzed mRNA levels of IL1RN and SASP factors by days in OIS system. The mRNA level of IL1RN considerably increases on day 6 from day 4 and then suddenly decreases on day 8 in OIS system (Figure 3-2-1). However, the mRNA levels of other SASP factors such as IL1α, IL1β, IL6 and IL8 on day 8 dramatically increase from day 6. It seems that the sudden decrease of IL1RN mRNA level induces dramatic increase of them based on the fact that the mRNA levels of them on day 6 are not quite high but abruptly increase after decrease of IL1RN mRNA level on day 8. It is assumed that the loss of IL1RN on day 8 gives more chances to other SASP factors to easily bind to IL-1R.

rIL1RN was purified and probed by anti IL1RA antibody (Figure 3-2-2). Concerning the half life of rIL1RN for its activity, rIL1RN was added every 2 days into culture media. The mRNA levels of SASP factors (IL1α, IL1β, IL6 and IL8) substantially decreased by 100μg/ml rIL1RN on day 8 from day 6 (Figure 3-2-3). This decrease substantiates the idea that IL1RN can regulate other SASP factors. It can also be confirmed that the sudden decrease of mRNA level of other SASP factors on day 8 is originated from the weakened inhibition capacity from the decreased production of IL1RN on day 8. This can also be

certified in IL1RN over-expressing cells. Compared to control, the mRNA levels of SASP factors decreased (Figure 3-2-4)

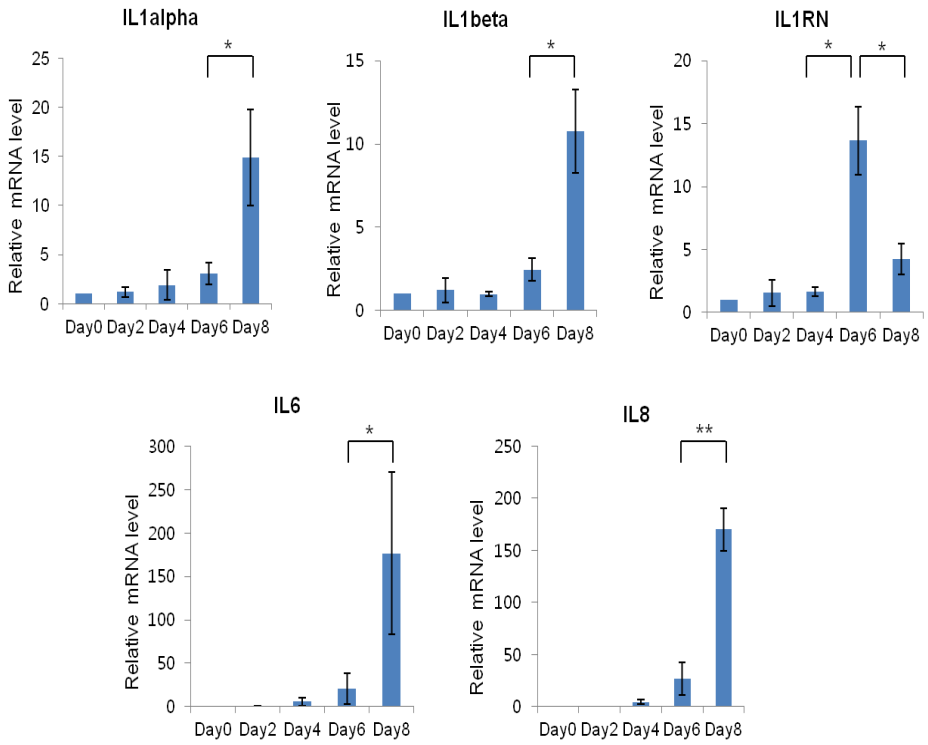


**Figure 3-2-1. IL1RN regulates other SASP factors in OIS system.**

Quantitative real-time PCR result showing that mRNA expression levels of SASP factors(IL1α,IL1β,IL6 and IL8) increased most on day 8 excepting for IL1RN. IL1RN secreted most on day 6 and then suddenly decreased on day8. Relative mRNA levels were normalized to day 0 as control *(* $P < 0.05$ **$P < 0.01$)*

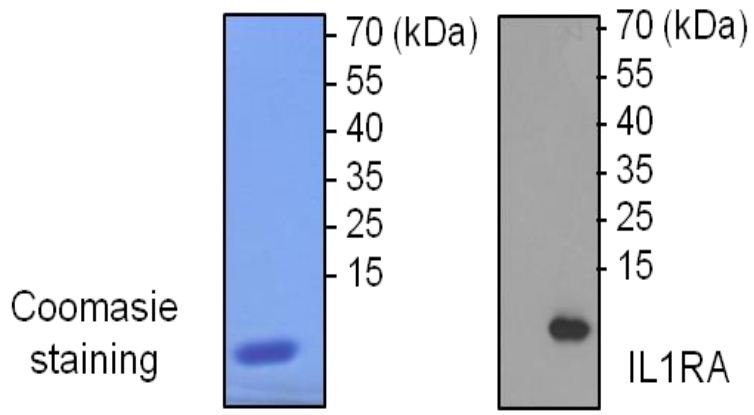


**Figure 3-2-2. Protein purification of recombinant hIL1RN.**

Recombinant IL1RN protein was purified followed by protocol and it was probed by anti-IL1RA antibody.

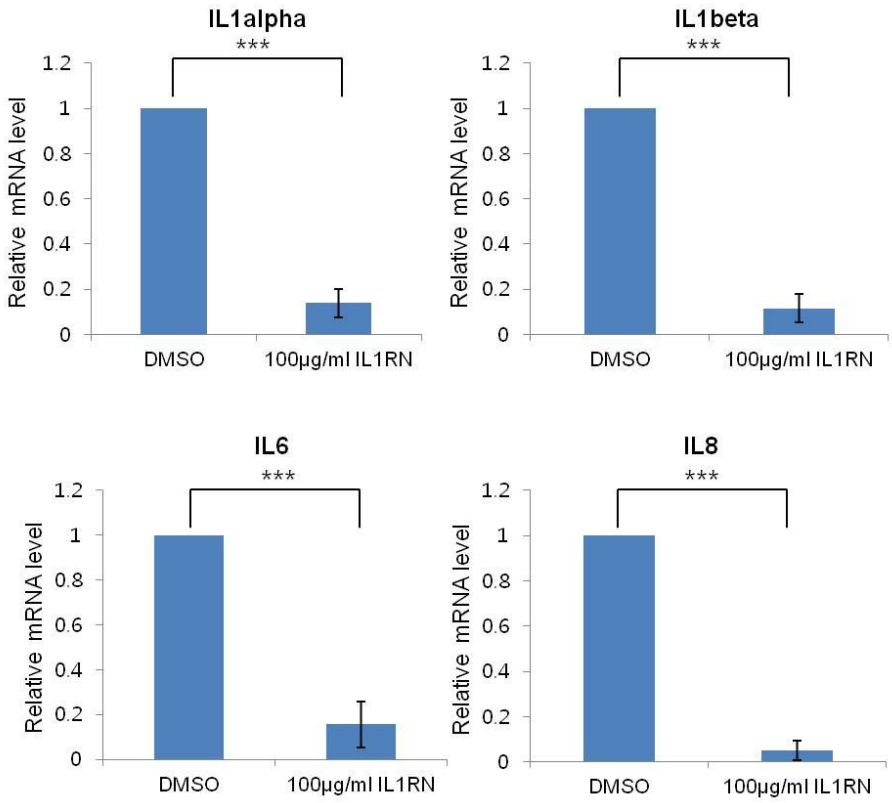


**Figure 3-2-3. The mRNA levels of SASP factors are decreased by 100μg/ml rIL1RN on day 8.**

The mRNA levels of IL1α, IL1β, IL6 and IL8 were dramatically decreased on day8 when 100μg/ml IL1RN was treated into cell culture media every two days concerning the half life of rIL1RN. DMSO was treated as control. Relative mRNA levels were normalized to control.*(***P < 0.001).*

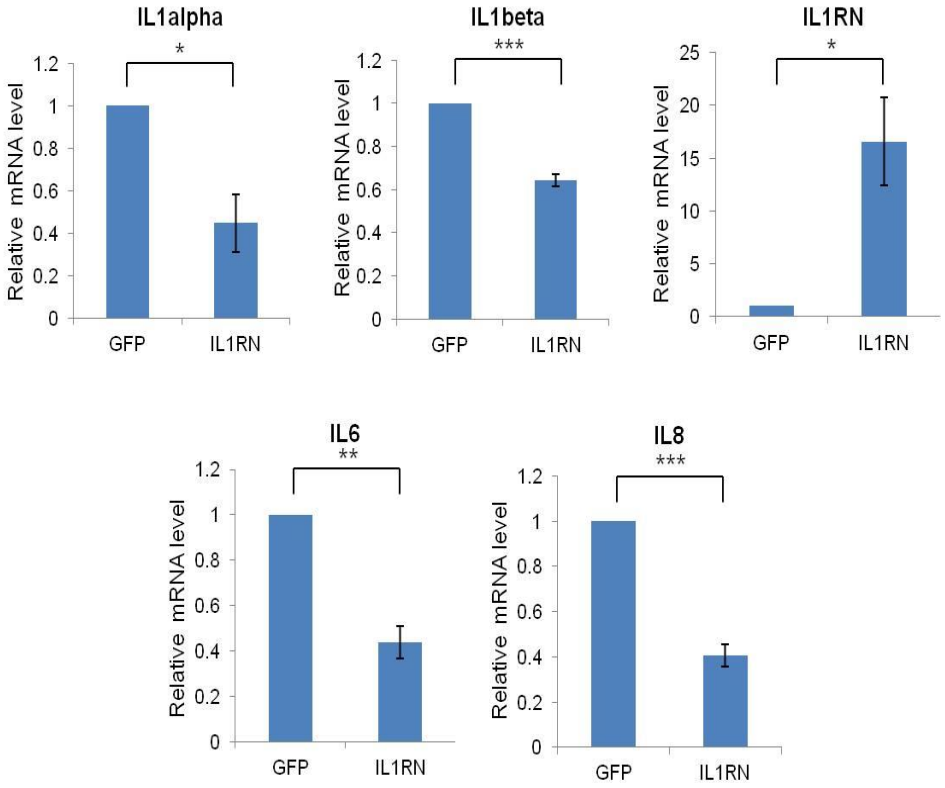


**Figure 3-2-4. The expressions of SASP factors other than IL1RN are decreased in IL1RN over-expressing cells on day 8.**

Quantitative real-time PCR result showing that mRNA expression levels of SASP factors(IL1α,IL1β,IL6 and IL8) had been decreased compared to control in IL1RN overexpressing cells on day 8. GFP expressing cells were used as control and relative mRNA levels were normalized to control *(* $P < 0.05$ ** $P < 0.01$ *** $P < 0.001$).*

### 3-3. IL1RN can attenuate senescence phenotype in OIS system.

To validate the clearance of SASP factors help attenuate cellular senescence, we performed SA-β gal assay to compare the amount of stained cells between control and rIL1RN added one. As the concentration of rIL1RN increases, the number of stained cells slightly decreases (Figure 3-3-1), showing that rIL1RN obstructs the binding of IL-1 ligands to IL-1 receptors. When we divided the number of stained cells by the whole number of seeded cells, the percentage of stained cells when rIL1RN was added decreased about fifty percent from control (Figure 3-3-2). When IL1RN is over-expressed, the result of SA-β gal assay was quite similar with when rIL1RN was added (Figure 3-3-3). The percentage of stained cells decreases compared to control with the same reason.

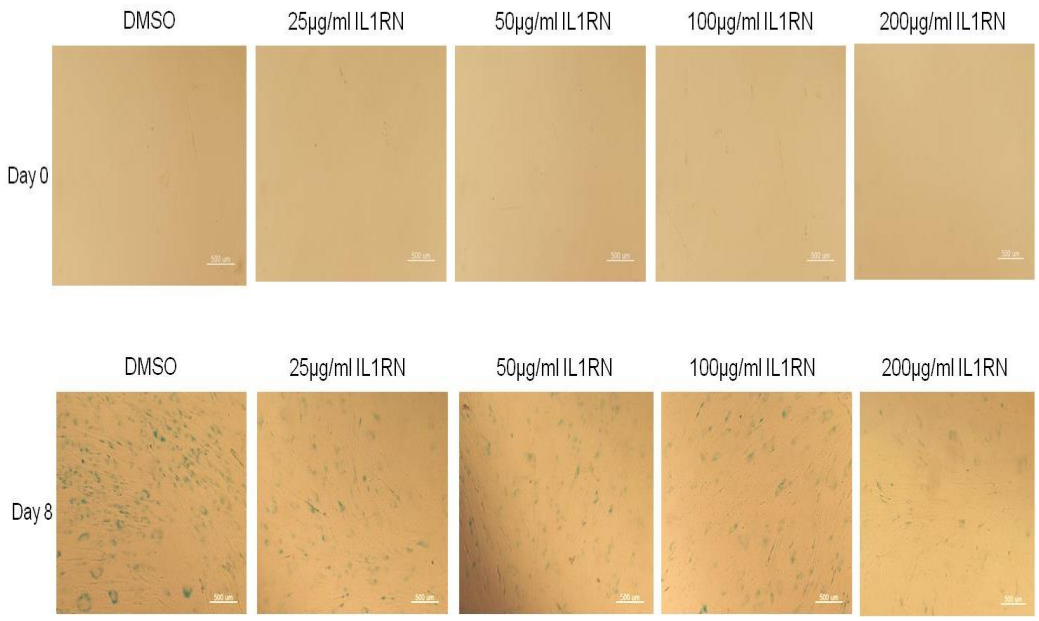


**Figure 3-3-1. IMR90 cells are stained less when the concentration of rIL1RN is higher in OIS system on day 8.**

Compared to day 0, cells were induced senescent on day 8 and the degree of staining depended on the concentration of rIL1RN.

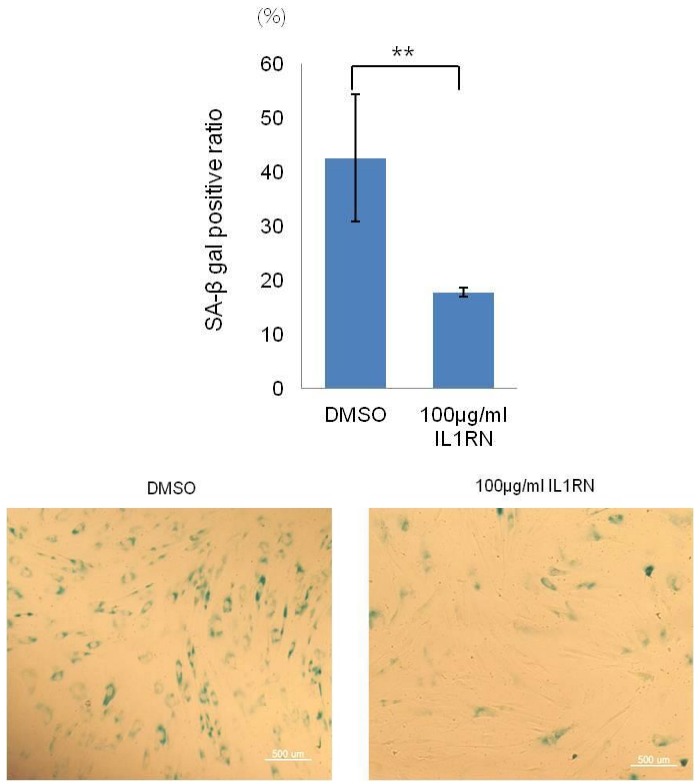


**Figure 3-3-2. The percentage of SA-β gal stained cells is decreased due to 100$\mu$g/ml rIL1RN on day 8 (10X, scale bar=500$\mu$m).**

Cells were stained fairly less when 100μg/ml rIL1RN was treated every two days on day 8. The SA-β gal positive ratio had been decreased about fifty percent from control. Stained cells were counted and divided by the whole number of seeded cells (n=5, $^{**}P < 0.01$ ).

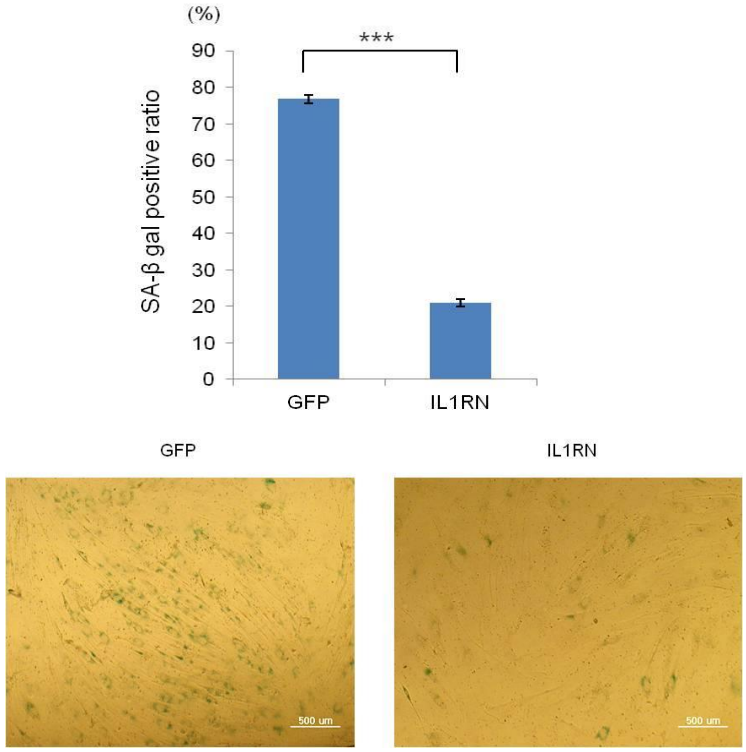


**Figure 3-3-3. The percentage of SA-β gal stained cells is decreased in IL1RN over-expressing cells on day 8 (10X, scale bar=500μm).**

Cells were stained fairly less in IL1RN overexpressing cells compared to control on day 8. The SA-β gal positive ratio had been decreased about seventy percent from control. GFP expressing cells were used as control. Stained cells were counted and divided by the whole number of seeded cells (n=5, ****P* < *0.001).*

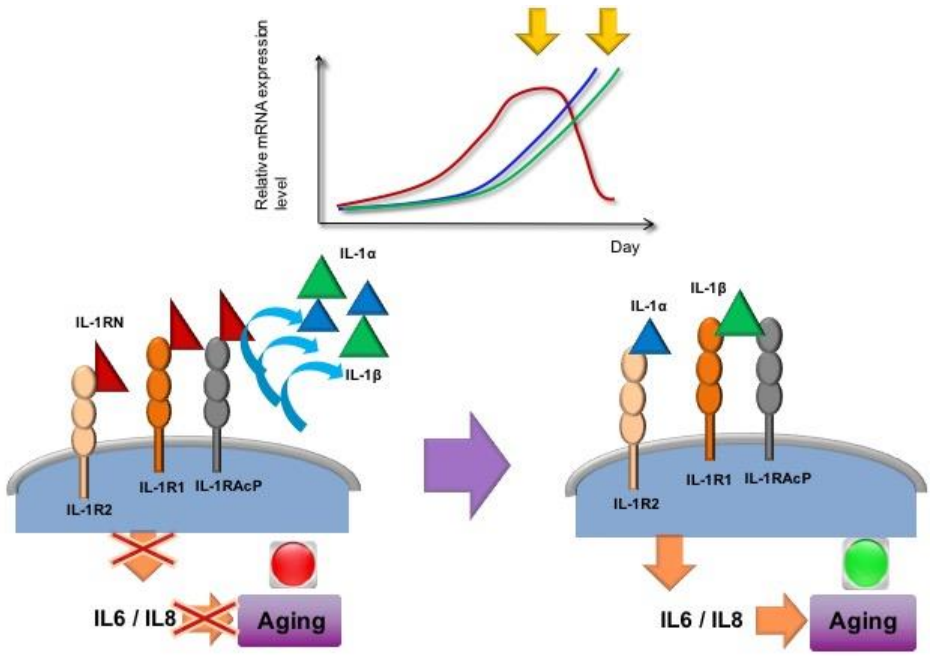


**Figure 3-3-4. A Schematic model.**

It was found that the expressions of SASP factors are regulated by IL1RN in OIS system. IL1RN has its own unique expression pattern in process of cellular senescence, which dramatically affects secretion of other SASP factors and cellular senescence at the same time.

# IV. DISCUSSION

Cellular senescence has been studied for quite a long time. However, the exact and multi-reciprocal interactions of processes leading to senescence are obscurely defined. In this study, we've analyzed mRNA levels of IL1RN and SASP factors by days in OIS system. We could find out some gene-expressional patterns affecting ongoing aging process exist. Especially, IL1RN known as an antagonist of IL1 receptor expresses in an interesting way which slightly increases till day 4 and drastically decreases on day 8. However, mRNA levels of SASP factors such as IL1α, IL1β, IL6 and IL8 go up till the end in oncogene induced senescent cells (Figure 3-2-1).

However, we questioned the meaning of its sudden decrease on day 8 and what would happen if it did not decrease. Now, it is assumed that the time point is the last effort of cell to suppress the over-production of SASP factors not to automatically pass on aging or apoptosis. However, the expression of IL1RN suddenly decreased on day 8, which leads to overproduction of SASP factors. This is very anti-tumorigenic reaction which is one of the main characteristics of cell-nonautomous SASP to cells because tremendously increased SASP factors such as IL6 and IL8 try to promote tumor suppression by driving the senescence growth arrest induced by activated oncogenes or oxidative stress (Kortlever et al., 2006; Acosta et al., 2008; Kuilman et al.,2008). On the contrary, if IL1RN did not decrease on day 8, it could be fatally tumor-promoting because of suppressed production of SASP factors. However, we expected to see attenuated phenotypes of senescence or aging due to clearance of those SASP factors attributed by prolonged production of IL1RN in this study.

Followed by results, mRNA expression of SASP factors such as IL1α, IL1β, IL6 and IL8 were quite suppressed till day 6 but suddenly increased on day 8. This is attributed by the decreased of IL1RN which prohibited binding of IL1 on IL1R on day 8. It is assumed that the decreased production of IL1RN gave more chances to other IL1 ligands to bind more to IL1R, which led stronger signaling to form a positive loop of IL1 signaling. It could also be confirmed by rIL1RN. The mRNA expressions of SASP factors on day 8 were dramatically decreased when rIL1RN was added compared to control (Figure 3-2-3), which explains the reason why their mRNA levels so increased on day 8 when mRNA level of IL1RN was decreased.

We could conclude that IL1RN can regulate the production of other SASP factors relying on its own expression pattern by passage. It is known that cell surface IL-1α is an upstream regulator of the senescence-associated IL6 and IL8 cytokine network (Arturo et al, 2009). However, it can also be said that not only IL1α but IL1RN which is an antagonist of IL1α also can be an upstream regulator of the network following its own expression pattern by passage in oncogene induced senescence system based on those results.

We could also assume that the clearance of SASP factors by IL1RN affected attenuation of senescence. Weaker stain was observed as the concentration of rIL1RN went higher through SA-β gal assay. On day 8, the percentage of stained senescent cells when rIL1RN was added were about fifty percent decreased compared to control (Figure 3-3-2). It was attributed from the reduction of accumulated amount of SASP factors by rIL1RN.

This phenomenon could similarly be observed in IL1RN over-expressing

cells. The mRNA expressions of IL1α, IL1β, IL6 and IL8 were certainly decreased in IL1RN over-expressing cells on day 8. In SA-β gal assay, IL1RN over-expressing cells were about fifty percent less stained than control. In conclusion, newly found significant role of IL1RN could be illuminated through this study. It was known as an antagonist of IL1 receptor. However, IL1RN has its own particular expression pattern in process of cellular senescence, which can regulate other SASP factors. The controlled SASP factors also can affect the process of cellular senescence, which gives a possibility of attenuation of senescence.

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# Ⅵ. ABSTRACT IN KOREAN

# 국문 초록

세포노화 현상에 대한 연구는 계속 되어져 왔지만 세포노화 과정을 조절하는 메커니즘에 대해 밝혀진 바가 거의 없는 것이 사실이다. 시간의 흐름에 따른 자연노화 현상 뿐 만 아니라 이번 연구에서는 유전자조절에 의한 세포노화현상과 노화과정을 촉진시키는 유전자조절 메커니즘에 초점을 맞추었다. 발암유전자를 이용해 cellular senescence 를 유도한 상황에서 날짜별로 IL1RN 과 SASP 인자들의 발현패턴을 분석해 보았을 때, IL1RN 의 유전자발현이 중간단계까지는 꾸준히 증가하다가 마지막 시점에서 감소하는 패턴임을 알 수 있었다. 만약 마지막 시점에서 감소하지 않았더라면 노화과정이 지연되지 않을까 하는 궁금증을 가지고 연구를 진행하였다. OIS 시스템에서 IL1RN 의 발현 패턴과 다르게 IL-1 signaling 과 관련된 IL1α, IL1β, IL6 와 IL8 같은 SASP 인자들은 마지막 시점까지 점차적으로 발현이 증가한다는 것을 알 수 있었다. 그러나 rIL1RN 이 첨가 되거나 IL1RN 이 과발현 될 때에는 SASP 인자들이 급격히 감소함을 볼 수 있었는데 이에 따라서 IL1RN 이 SASP 인자들의 분출을 조절한다는 결론을 내릴 수 있었다. 이 뿐 아니라, IL1RN 에 의한 유전자 조절이 세포의 노쇠현상에 영향을 끼칠 수 있다는 것을 SA-β gal 분석을 통하여 알 수 있었다.

이번 연구는 SASP 인자들의 억제가 세포의 노쇠과정 지연에 영향을 끼칠 수 있다는 가능성을 제시해준다.

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**주요어: IL1 signaling, IL1RN, Cellular senescence, SASP**

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